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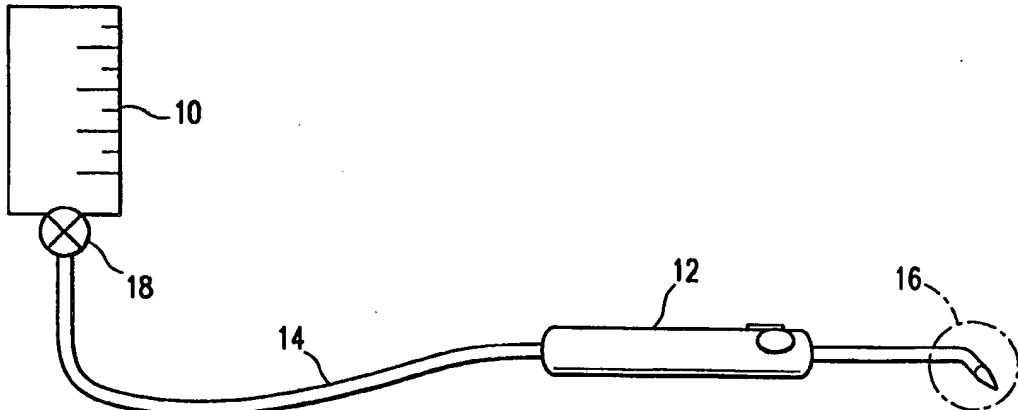


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(54) Title: **DELIVERY OF AN ANGIOGENIC SUBSTANCE**



(57) Abstract

Using either a percutaneous, intraoperative or minimally invasive approach, an elongated member containing an angiogenic agent is guided to a heart wall and the agent is dispensed into heart tissue. The administration of the angiogenic agent can be automated and controlled so as to be synchronized with respect the cardiac cycle. The device has a distal end configured to dissect heart tissue and penetrate into the myocardium. Additional fluids or substances can be dispensed in combination with the angiogenic agent to provide visualization and site mapping. In certain embodiments, the angiogenic agent is delivered adjunctively with the administration of energy, such as laser energy or RF energy which disturbs the heart tissue sufficiently to enhance the effects of the agent. There is also disclosed a device for administering an angiogenic agent that contains the angiogenic agent and additional fluids such as a marker within a single conduit.

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DELIVERY OF AN ANGIOGENIC SUBSTANCEFIELD OF THE INVENTION

The present invention relates to methods and apparatus for the delivery of substances to tissue, and in particular to ischemic myocardial tissue of a patient's heart, either percutaneously or intraoperatively. The delivery of the substances may either be adjunct to transmyocardial revascularization (TMR) or another procedure, or may constitute a procedure in and of itself.

BACKGROUND OF THE INVENTION

Coronary artery disease affects the lives of millions of patients worldwide. Many therapies are available for atherosclerosis, including coronary artery by-pass graft surgery (CABG) to bypass blocked arteries, percutaneous transluminal coronary angioplasty (PTCA) interventions to attempt to restore patency, the implantation of stents that attempt to maintain patency, the use of atherectomy to remove collected plaque, and a number of pharmacological approaches that attempt to reduce the effects of narrowing of blood vessel lumens by the stenosis by reducing the amount of plaque or by altering the hemodynamic characteristics of the patient's blood. While the aforesaid procedures provide well known clinical improvements, none provide a fully satisfactory long term therapy. The presently available pharmacological therapies are of limited value. Ideally, a non-invasive pharmacological or genetic therapy would facilitate reperfusion of ischemic myocardium, either by restoring patency or by creating new blood vessels in the ischemic region.

A number of different substances and techniques are known for attempting to treat coronary artery disease by the administration of a therapeutic substance to a patient. One common method of administration is systemic administration. For example, EPO Application EP 314105 discloses 5 the oral administration or intramuscular injection of an "angiogenesis enhancer". U.S. Patent No. 5,480,975 discloses treating hypoxic tissue damage by local or topical administration of a transition metal compound to induce VEGF expression. The indirect nature of these routes of administration, however, are generally less desirable and not universally applicable to all 10 forms of substances that might be used to treat ischemic myocardium.

Using a catheterization procedure to deliver a substance to the vessels in the vicinity of the stenosis is also known. For example, PCT Application WO 9723256 discloses the percutaneous delivery of an angiogenic factor to a vessel wall through the lumen of a catheter. The distal end of the catheter is 15 provided with infusion ports that engage the vessel wall when the catheter is expanded, and infusion may be enhanced by providing needles or other penetrating elements. U.S. Patent 5,681,278 discloses treating vascular thrombosis and angioplasty restenosis by administering a bioactive agent to an extravascular treatment site, particularly introducing such an agent 20 proximally adjacent to the exterior of a coronary artery. U.S. Patent No. 5,698,531 discloses the site specific installation of cells or the transformation of cells by delivering proteins by catheterization to discrete blood vessel segments, wherein the agent is situated on the walls of the blood vessel or

perfused in the tissue of the vessel. U.S. Patent No. 5,523,092 discloses an indwelling catheter for localized delivery of a substance into a "tissue conduit" without disrupting the fluid flow. U.S. Patent No. 5,244,460 discloses the intracoronary arterial delivery of a blood vessel growth promoting peptide 5 periodically over several days.

Recent advances in biotechnology have shown promise for treating coronary artery disease. In *Circulation* 1998;97:645-650, Schumacher et al. report treating coronary heart disease using human growth factor FGF-I (basic fibroblast growth factor) to induce neoangiogenesis in ischemic myocardium. 10 The FGF-I was administered during a CABG procedure by injection into the myocardium distal to the IMA/LAD anastomosis and close to the LAD. The results reported demonstrate the efficiency of FGF-I treatment. However, the FGF-I administration was made by direct injection during surgery which is less than optimal because it is as invasive to the patient as a CABG procedure. In 15 addition, at least one fibroblast growth factor has been delivered by using a microparticle carrier that is delivered to an artery via a catheter in a non-ischemic model, as reported in *Nature Biotechnology* 1998; 16:134 and 159-160. The intra-arterial delivery of microparticles produced positive results, but was chosen so that the surrounding tissue would be undamaged. The article 20 states that non-invasive techniques to deliver genes into peripheral ischemic myocardial tissue are presently unavailable.

Thus, there exists a long felt, yet unmet need for methods and apparatus that permit the localized introduction of a substance into the

myocardium directly, either during an intraoperative procedure or percutaneously.

In addition to these advances in biotechnology, coronary artery disease is also successfully treated by transmyocardial revascularization (TMR), using 5 methods and apparatus such as those disclosed in U.S. Patent Nos. 5,380,316; 5,389,096 and 5,554,152, all of which are incorporated herein by reference. During TMR using intraoperative, minimally invasive or percutaneous approaches, energy is delivered directly to the myocardium, preferably in or near to the ischemic area, and as a result a focal injury occurs. 10 This focal injury is often in the form of a "channel" formed by the laser, although the size of the channel and energy used to create the tissue disruption can vary. Additionally, the degree of patency of the channel and the amount of tissue ablated to form the channel may also vary. It has been found that the focal injury acts to stimulate subsequent neovasculogenesis. 15 Moreover, in addition to the eventual reperfusion of the ischemic region, there is evidence that the disruption of certain afferent nerves in the tissue and other effects provides both acute and chronic reduction in angina pain.

The use of TMR in conjunction with the administration of localized agents is disclosed in co-pending U.S. patent application Ser. No. 438,512, 20 filed June 7, 1995 which is assigned to the assignee of the present invention and the entirety of which is incorporated herein by reference. This application discloses the administration of therapeutic and diagnostic agents into the myocardium, and particularly in conjunction with TMR procedures.

[Additionally, co-pending U.S. patent application Ser. No. __, __, filed on even date herewith, which is assigned to the assignee of the present invention, the entirety of which is incorporated herein by reference, discloses a catheter system that is useful for placing a payload within a specified portion of a patient's heart chambers, and most particularly within the left ventricle (LV), an area where revascularization is often indicated.]

There still exists, however, a need for improved apparatus and improved techniques that will permit the adjunctive delivery of substances into localized regions within the myocardium efficaciously, efficiently and in a manner that can enjoy widespread adoption by the medical profession, such as cardiac surgeons and interventional cardiologists.

SUMMARY OF THE INVENTION

The foregoing objects are achieved by the present invention. In accordance therewith, the apparatus delivers a substance, such as an angiogenic agent to a desired tissue region. In one presently preferred embodiment, an elongated device has a handpiece for delivering a metered dose of a substance via a delivery lumen. The elongated device may be either a catheter or an intraoperative probe, and in certain preferred embodiments has a reservoir containing the substance in a deliverable state, such as an angiogenic agent. Preferably, the device comprises a metered dispensing apparatus for injecting one or more appropriate doses and includes a dispensing control system, such as a switch disposed on the handpiece or a separate foot pedal. In some embodiments, the dispensing control system is automated, and preferably, a signal generated by the heart is provided to a circuit synchronizing the activation of the automated dispensing apparatus to the cardiac cycle. For example, the apparatus may be synchronized to the patient's ECG by a circuit which inhibits activating the dispensing apparatus during a pre-determined portion of the cardiac cycle.

In most embodiments, the delivery device has a distal end which is configured for penetration into the patient's tissue, e.g., has a sharp or needle-like distal end, and has at least one orifice in fluid communication with a lumen extending through the distal extremity of the device which is in fluid communication with the one or more orifices and a source of therapeutic or diagnostic substance. Additionally, in certain embodiments, the distal end has

one or more radially oriented lumens to direct the substance to be delivered laterally within the patient's tissue. Another aspect of certain embodiments of the present invention relates to contacting the tissue to be treated with the distal end. For example, elongated elements such as bristles or barbs may be 5 provided that deploy from a first position inhibiting tissue contact to a second position permitting tissue contact are provided in some embodiments. Preferably, the elongated elements are aligned with a longitudinal axis of the device and disposed along an outside surface so they deploy from a first position that inhibits tissue engagement to a second position that permits 10 tissue engagement. In other embodiments, the distal end can have an enlarged or bulbous section, which may or may not be expandable.

Other aspects of certain embodiments of the present invention include providing the device with a radiopaque marker disposed at the distal end to aid in the fluoroscopic visualization thereof during the procedure and providing 15 a depth stop to limit device penetration depth. One preferred embodiment of a depth stop is the construction of a section of the distal end smaller in diameter than a second section immediately proximal of the distal section and a shoulder connecting the distal section and the second section that acts as the depth stop. Alternatively, the depth stop can be one or more mechanical 20 elements or arms that extend out radially from the distal end. In other embodiment, visualization of the dose is accomplished by the administration of a marker substance either along with or in addition to the therapeutic substance such as an angiogenic agent. In another aspect of the present

invention, multiple lumen catheters or probes are provided with one of the plurality of lumens being used to deliver the substance such as an angiogenic agent, while other lumens may be utilized to deliver other fluids, substances, or apparatus.

5 In certain embodiments, the present invention may also be provided with a distal tissue contact device for energy delivery to the myocardium to perform a procedure that dissects, disturbs, disrupts or ablates the tissue region to which the substance is injected. The distal tissue contact device may be one of a number of known apparatus whereby energy is delivered to 10 the myocardium to perform a procedure that dissects, disturbs, disrupts or ablates the tissue. For example, the distal tissue contact device can be a mechanical device affixed to the distal end, or it can be a device such as a laser energy conductor, an RF energy conductor, an ultrasound transducer, or a current conductor. In another preferred embodiment, the distal tissue 15 contact device can be a lumen in a device connected to a source of fluid at a pressure and velocity sufficient to disrupt tissue. In any of these embodiments, the distal tissue contact device is preferably introduced using a lumen separate from a lumen carrying the therapeutic or diagnostic substance to be delivered.

20 Thus, one preferred embodiment of the present invention broadly discloses an injector apparatus synchronized to a cardiac cycle signal that has a conduit with a least one lumen connected on a proximal end to an injection device and, preferably, a solenoid connected to the injection device. In use,

a controlled amount of a substance to be delivered is dispensed when the solenoid is pulsed by a signal related to the cardiac cycle. Preferably, the solenoid advances the same amount after each of one or more pulses, so that more than one injection can be given in each heartbeat if desired. When an 5 embodiment including a distal tissue contact device is used, an activation switch is also provided and energy is introduced into the heart tissue by operation of the activation switch, preferably but not necessarily in synchronization with the cardiac cycle.

Another additional aspect of the present invention is the provision of an 10 apparatus for delivering a bolus of substance that has a delivery lumen extending from a distal end to a proximal point distal to the proximal end, and wherein at least a first section of the delivery lumen is filled with the substance to be delivered. In certain embodiments a second section of the delivery lumen in fluid communication with the first section is provided that 15 contains a second substance other than the first which may aid in delivery or visualization of the first substance when it is delivered. In any embodiment, it is preferred, though not required, that the substance, i.e., an angiogenic agent, is in a fluidic or thixotropic state to facilitate delivery. In one presently preferred embodiment, the delivery lumen contains at least an angiogenic 20 agent and a marker substance.

Although it will be readily understood that the percutaneous and intraoperative versions of the present invention may differ markedly in construction, each device may have one or more of a number of features

addressed below. The discussion of these features of a substance delivery system is thus not specific to or limited to either the percutaneous or intraoperative embodiments.

As used herein, the term "angiogenic agent" includes any material or substance useful in a procedure that promotes the growth of new vessels, particularly the growth of new vessels in the myocardium, however, it will be understood that an angiogenic effect is useful in other organs, such as the liver and kidneys. The methods and apparatus of the present invention may employ a wide variety of angiogenic agents, including small molecule drugs, active compounds and cellular and gene therapy agents. Examples of active compounds include, by way of non-limiting example, biologically active carbohydrates, recombinant biopharmaceuticals, agents that are active in the regulation of vascular physiology, such as nitric oxide agents that effect the regulation of gene activity by modulating transcription, the turnover of cellular mRNA, or the efficiency with which specific mRNA is translated into its protein product, i.e., antisense pharmaceuticals. Other active compounds include hormones, soluble receptors, receptor ligands, peptides (both synthetic and naturally occurring), peptidomimetic compounds, specific and non-specific protease inhibitors, postaglandins, inhibitors of prostaglandin synthase and/or other enzymes involved in the regulation of prostaglandin synthesis, growth factors that affect the vasculture such as the fibroblast growth factors (FGF's), acidic (aFGF, FGF-II) and basic fibroblast growth factors (bFGF, FGF-I), vascular endothelial growth factors (VEGF), angiogenin,

transforming growth factor alpha, and transforming growth factor beta. The foregoing list is meant to illustrate the breadth of angiogenic agents and other substances useful with the present invention and is not meant to be exhaustive or in any way limit the scope of the invention. It is contemplated that there are classes of angiogenic agents possessing structures significantly similar to other molecular agents, and that these agents will have specific biological activities associated with them while being deficient in other biological activities that are less desirable therapeutically. Any and all of the angiogenic agents useful with the present invention may comprise substantially pure compounds, defined or relatively less well defined admixtures of compounds, such as those that might result from a biological system such as conditioned serum or conditioned cell culture media.

Finally, any reference to "angiogenic agent" herein will be understood to include diagnostic agents and markers useful with the present invention. Such diagnostic agents or markers may be delivered before, after or during the administration of the angiogenic agent itself, and include any substances used to ascertain the physical location, configuration or physiologic state of a tissue or tissues, e.g., dyes, stains, diagnostic challenge agents and agents such as radiopaque agents used to enhance contrast during diagnostic or therapeutic procedures such as myogenic compounds, anesthetic agents or chemical sympathectomy agents.

The various features and advantages of the invention will become more apparent from the following detailed description of the invention when taken in conjunction with the accompanying exemplary instructions.

BRIEF DESCRIPTION OF THE DRAWINGS

5 FIG. 1 is a perspective view of one preferred embodiment of an intraoperative system for administering a therapeutic substance.

FIG. 2 is a perspective view of one preferred embodiment of a percutaneous system for administering a therapeutic substance.

10 FIG. 3 is a diagrammatic illustration of a control system useful with the embodiments of the present invention illustrated in FIGS. 1-2;

FIG. 4 is a partial side elevation view of the distal tip of a device embodying features of the present invention.

FIG. 5 is a partial side elevation view of the an alternative construction of a distal tip of a device embodying features of the present invention.

15 FIG. 6 is a partial side elevation view of the an alternative construction of a distal tip of a device embodying features of the present invention.

FIG. 7 is a partial side elevation view, partially in cross-section, illustrating the embodiment of FIG. 6 within the lumen of a catheter or guide.

20 FIG. 8 is a partial side elevation view of the an alternative construction of a distal tip of a device embodying features of the present invention.

FIG. 9 is a partial side elevation view of the an alternative construction of a distal tip of a device embodying features of the present invention.

FIG. 10 is a partial side elevation view of the an alternative construction of a distal tip of a device embodying features of the present invention.

5 FIG. 11 is a partial side elevation view of the an alternative construction of a distal tip of a device embodying features of the present invention shown after penetration into the myocardium.

FIG. 12 is a partial side elevation view, partially in cross-section, of the an alternative construction of a distal tip of a device embodying features of the present invention.

10 FIG. 13 is a partial side elevation view of an alternative construction of a distal tip of a device embodying features of the present invention.

FIGS. 14-15 are cross-sectional views of alternative multiple lumen catheters useful with certain embodiments of the present invention;

15 FIG. 16A is a partial side elevation view of the distal tip of a device embodying features of the present invention shown penetrating the myocardium;

FIG. 16B depicts the apparatus of FIG. 16A after deeper penetration into the myocardium;

20 FIG. 17 is a partial cross-sectional elevation view of a conduit carrying an angiogenic agent and other substances useful in conjunction with the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Reference is made to FIG 1 which depicts a basic system for the intraoperative administration of an angiogenic substance. As illustrated, a distal reservoir 10 for the substance to be delivered is in fluid communication with a distal administration device 12 via a fluid conduit 14. The distal end 5 16 of the administration device 12 includes a specialized distal tip construction that will be described in further detail below. A valve 18 is provided to control the flow of substance from the reservoir 10 to the conduit 14. The substance to be delivered by the methods and apparatus of the present invention may be stored either proximally or distally. A number of 10 different delivery device constructions are useful for each case. In most embodiments, however, the fluid conduit 14 will comprise a hypodermic tube formed of suitable metal such as stainless steel or similar material. In certain embodiments, the conduit 14 may serve as a carrier and reservoir for the substance. In such embodiments, the conduit 14 will be formed into a coil to 15 provide for longer "storage length," and thus permit it to serve as a reservoir of greater capacity. In such embodiments a separate reservoir 10 illustrated may not be required. Additionally, in other embodiments, a reservoir can be built into the distal end 16 of the device 10, particularly for those instances where the volume of substance to be delivered is extremely small.

20 FIG. 2 illustrates a percutaneous system similar to FIG. 1 which has a proximal catheter controller 20 and catheter 22. The catheter 22 terminates in a distal administration tip 24. As explained above, the substance reservoir

10 and connecting fluid conduit 14 may not necessarily be present in each embodiment of the percutaneous system.

In the case of either FIG. 1 or FIG. 2, the basic function of the present invention will be to place the distal tip in contact with, or at least in close proximity to, the surface of the tissue to be treated such as in the patient's heart tissue. The surface may be the endocardium, epicardium, or the myocardium, if either the endocardium or epicardium have been pierced. The placement of the distal tip will permit myocardial delivery of a bolus of angiogenic agent, preferably by injection, after the distal tip has penetrated 10 the myocardium.

Another aspect of the present invention is illustrated diagrammatically in FIG. 3. In preferred embodiments, the penetration of tissue of the heart 30 by the distal tip 32 (from either side, the epicardial side being illustrated) will be followed by substance injection. Preferably, the substance injection is automated and an automatic administration device 34 (labeled ADMIN) will dispense a pre-selected amount of substance to the site where the distal tip 32 has penetrated. The activation of the automated administration device 34 may be accomplished via a foot switch (not shown), handpiece switch (not shown) or via another system. The automated system as shown in FIG. 3 has 20 a signal line 36 which is connected to an electrocardiograph (ECG) 38 or similar device for measuring the cardiac cycle. The ECG 38 in turn is connected to the ADMIN device 34. The dispensing of a dose is initiated upon a predetermined set of cardiac parameters once an activation signal is

received from a foot switch, handpiece switch or other device indicating that the operator has properly positioned the distal end of the device. As known in the art, the ECG signal can be coupled to a device controller and can be used to permit or inhibit an invasive activity, such as the firing of a laser, 5 during periods of the patient's heart cycle to minimize the possibility of fibrillation or other arrhythmia. In the use of the present invention, it will also be preferable in some embodiments when using certain angiogenic agents to similarly enable administration of the substance during a safe period of systole or inhibit the administration of an automated dose outside the safe period. 10 Additionally, by synchronizing substance injection to the ECG, a consistent value of pre-load force between the distal end 32 and the tissue of heart 30 will be achieved since the spatial relationship between the administration device and the heart will be similar at a particular point over several cycles.

Thus, in one preferred embodiment, an injector that is synchronized to 15 the heartbeat is provided by connecting a syringe or similar administration device 34 to the distal end 32, as described above. A solenoid plunger (not shown) within the administration device 34 is connected to the syringe so that when the solenoid is pulsed with electrical energy, the syringe is quickly advanced a finite distance, resulting in the injection of a controlled amount of 20 substance. A DC solenoid can be pulsed with a voltage much higher than the normal DC constant operating voltage, providing the force required to quickly move a tiny amount of viscous material down a narrow lumen. The pulse for the solenoid is preferably synchronized to the heartbeat. In certain

embodiments, a variable delay circuit can be added to adjust the synchronization point to the heart cycle. Numerous other timing and control circuits can be devised to carry out the same function.

As explained above, in certain embodiments, either the handpiece 20 or 5 the proximal controller 30 may include one or more switches or activation devices that control the functions of the system, or such functions can be controlled by a foot switch or other apparatus. An additional function that is preferably controlled is the advancement of the distal end 34 into the patient's heart tissue, as well as the discharge of a bolus of the substance 10 into such tissue. In certain embodiments, the sharp end of the device will be advanced into the tissue while a catheter or probe remains in place. The advancement of the sharp end is preferably controlled and linked to the administration, either mechanically or by control logic, or both.

In those embodiments where a percutaneous system is used and the 15 injection is at or beneath the endocardial surface, the issue of knowing that the injector tip is in contact with the endocardial surface arises. In such embodiments, an indication of tip contact is preferred to ensure that the substance is administered into the endocardium and underlying myocardium, and not into ventricular blood. Thus, an additional signal that can be 20 interconnected with the administration device 34 is a tip contact signal, and administration is preferably inhibited when there is no tip contact.

In addition to the basic parameters set forth above, those skilled in the art will appreciate that a number of practical factors may control design

details of devices made in accordance with the present invention. For one, the cost per dose of the substance delivered may be a determinative factor as to whether wasting the delivered substance is a threshold issue. A related issue is medical safety and efficacy of the substance delivered. For various 5 angiogenic agents, the precision of dose needed is likely variable, and the deleterious effects, if any, of excess delivered substance being deposited or administered into the blood and carried off without side effects must be determined for each substance on a case-by-case basis. Additionally, the ease in which the angiogenic agent is delivered may be related to the viscosity 10 of the fluid in which the substance is delivered. In some cases, it may not be possible to alter the viscosity, one reason being that a particular concentration of substance is necessary for efficacy and as a result the viscosity is higher than would otherwise be optimal for delivery. Whether it is altered or not, it is anticipated that the viscosity of angiogenic agents and other fluids that are 15 delivered in procedures according to the present invention will vary over a wide range from lower than that of water to significantly higher. Thus, the term "fluid" as used herein is to be construed in its broadest sense and thus may be a gas, a colloidal suspension, a gel and further encompasses embodiments where the angiogenic agent is made into a solid or semi-solid 20 and carried or moved by the action of another fluid, or by mechanical force at the end of a column of microspheres or even larger "pellets" or agglomerations of solids. As known by those skilled in the art, each of these forms can be delivered, but they may create a unique set of delivery problems

which can be readily solved once the fundamental parameters of the delivery are established.

Similarly, the pharmacokinetics of the angiogenic agent are also a factor in determining how the delivery of the angiogenic agent is to be made.

5 In other words, even if the identical delivery apparatus is used, a change in angiogenic agent may require a change in the velocity and pressure by which the substance travels within the delivery lumen in the device to the distal end thereof. In some instances, if the velocity and pressure are too great, leakage of the angiogenic agent around the injection site may occur, or unintended or

10 excessive tissue damage may occur. If the administration or injection rate is insufficient the heart may become irritated, position may be lost, or the procedure may be unnecessarily lengthened. Thus, for each substance, pharmacokinetic determinations need to be made. For example, when a sub-endocardial injection is made the contractility of the tissue will cause a certain

15 amount of a particular angiogenic agent to be expressed from the site of deposition, depending upon the viscosity and other factors. In some cases, where a longer residence time is necessary, this effect will be detrimental, whereas other angiogenic agents possessing a higher affinity and thus requiring a shorter residence time will be taken up relatively quickly and

20 efficacy will not be diminished by this phenomenon. These determinations, however, are easily and effectively made using known techniques that will not require undue experimentation. Thus, to control the administration of the angiogenic agent in, for example, embodiments where it is important to

reduce or eliminate waste or accidental discharge of excess material into the bloodstream, a variety of well known solutions such as one-way valves, metering valves and other apparatus that handle and control the flow of the fluid from a reservoir to the tissue will be incorporated into the apparatus.

5 The present invention provides methods and apparatus to localize the injection of angiogenic agents. For example, the injection site and the growth of the angiogenic vessels in the direction that will provide the most beneficial effect is more likely via an injection near the occlusion rather than a retroperfusion delivery by injection in the coronary sinus. This localization is 10 difficult if the arterial disease is diffuse. Finally, at least in the case of some angiogenic agents like VEGF, it is not clear that the administration of growth factors alone will mediate large vessel growth. Thus, intramyocardial delivery will be advantageous over the intracoronary delivery described above.

15 As was the case with the overall system described above with reference to FIGS. 1-3, there are a number of useful embodiments for the distal end of the devices of the present invention. In most embodiments, the distal end of a device is configured to readily penetrate at least a few layers of tissue cells.

20 Referring now to FIG. 4, one preferred embodiment of a distal end 40 is shown. In the construction of the distal end 40 illustrated it has a simple sharp tip 42 to permit the flow of angiogenic agent, as illustrated by the arrows. A radiopaque band 44 is also preferably provided. The distal end 40 preferably perforates the endocardium in the percutaneous embodiment, or

the epicardium in the intraoperative embodiment, and then holds its place while a bolus of substance is directed into the tissue. In one exemplary embodiment, the dosimetry of the substance is 100 μ l per injection at 10 injection sites, and the inner diameter of the delivery tube is about 0.018 inches (0.46 mm). In such an embodiment, the substance doses for the ten injection sites would take up a significant length of the delivery tube and would usually require a reservoir. Additionally, in such a case, the retention of the distal end 40 in place is important. In certain preferred embodiments, structural elements such as those described in further detail below keep the 5 distal end properly positioned and engaged during substance delivery.

10

As shown in FIG. 5, the distal end 50 can be modified by introducing radial orifices 52. The central lumen may remain open, or may be closed. In the latter case, the radial orifices 52 will provide the only path for flow into the myocardium and will thus tend to force the angiogenic agent over a wider 15 area lateral to the injection site than the bolus delivery as with the distal end shown in Fig. 4. Additionally, in preferred embodiments, the sharp 54 itself or other structures associated with the distal end 50 preferably possess shape memory and/or are comprised of stainless steel, NITINOL, or other materials known in the art to have such characteristics. Glass and high strength plastic tubing may also be employed. A radiopaque band 56 may be provided as 20 with the previously discussed embodiments.

Referring now to FIG. 6, another embodiment of an apparatus made in accordance with the present invention is shown. In this embodiment the

distal end 60 has one or more sharps 62 and 64 in the form of "bristles" or needles that extend generally radically or along a curved, radially outwardly extending path or spiral. These sharps 62 and 64 are preferably deployed when the distal end is located at a specific site and would engage the heart 5 wall or other portion of the vasculature. In some preferred embodiments, the bristles may be hollow to provide conduits for the delivery of the angiogenic substance via those lumens, as shown by the arrows in FIG. 6. Alternatively, the sharps 62 and 64 are solid and serve as fixation elements for a larger needle 66 that defines the delivery lumen, as explained above with reference to FIGS. 4-5. FIG. 7 illustrates a preferred delivery of the distal end 60 shown in FIG. 6. As shown, the bristles 62 and 64 are preferably collapsed against the body of the distal end 60 by delivering the device within a catheter or sleeve 68. Delivery in this manner prohibits unwanted dissection or other damage to tissue that is not being treated. A radiopaque band 69 10 may be provided as shown for fluoroscopic observation thereof when disposed within the patient.

Another embodiment of the present invention illustrated in FIG. 8. includes a distal end 80 with a sharp 82 that is helically shaped. Such a distal feature will aid in the retention of the distal end 80 in the tissue during 20 administration of the angiogenesis agent. The construction shown in FIG. 8 includes either diffusion ports 84 along the sharp 82, or diffusion ports 86 along other portions of the distal end structure 80, or both, as illustrated. As explained with reference to FIG. 5 above, such ports will aid in the lateral

diffusion of the angiogenic agent or other substance into the tissue surrounding the distal end 80 when disposed within the heart tissue. A radiopaque marker 86 may also be provided.

Referring now to FIG. 9 an additional embodiment of fixation devices useful in the present invention are illustrated. As shown, the distal end 90 has several moveable barbs 92. As with the radial or spiral extensions discussed above with reference to FIGS. 6-8, the barbs 92 are preferably moveable so they will not interfere with the placement of the distal end of the device within the patient's tissue. After placement, the barbs 92 are preferably deployed by being pushed outwardly by liquid exiting through one or more lateral orifices 94 in the distal end 90 as shown by the arrows in FIG. 9. This deployment via fluid pressure may occur just prior to, or simultaneous with the delivery of angiogenesis substance. The barbs 92 help to keep the distal end 90 engaged in the myocardium during substance delivery. Preferably, the barbs 92 are retractable so that they are covered when the inner catheter or delivery tube is pulled inside a guide catheter or sleeve, as discussed above with reference to FIG. 7. Alternative constructions to the barbs 92 include a back cut "sawtooth" or "rasp" structure lying longitudinally along the sides of the exterior wall of the distal end, which may either be retractable as shown in FIG. 9, or may be fixed, as were the bristles 62 and 64 shown in FIG. 6.

In addition to deploying structural elements, the movement of the angiogenic agent or other fluid can additionally be useful to help ensure

retention of the sharp and aid in dissection and diffusion. As shown in FIG. 10, in certain embodiments, the distal end 100 has angled orifices 102 which are selectively arrayed within the distal end construction so that the directionality of the substance flow is altered as shown by the arrows. The 5 resultant force will tend to retain the distal end 100 in place, rather than dislodge it, or in some cases will actually drive the distal end deeper into the tissue. As shown, it may be necessary to provide an orifice 104 at the tip in order to regulate the effect of the rear facing orifices 106.

Another embodiment of a mechanical fixation device useful with the 10 present invention is shown in FIG. 11. In this embodiment, the distal tip 110 comprises a "bulge" 112 or similar enlarged structure that represents a large diameter proximal of the distal tip. In certain embodiments, the bulge 112 may be expandable like a balloon so that it is trapped in place by friction with the swelled tissue. The expansion and contraction of the bulge can be 15 controlled by the administration of the angiogenic agent, or by using multiple lumens, as described above, such that a dedicated lumen provides insufflation fluid. Alternatively, in some embodiments, a non-expanding distal "bulge" 112 may be permanently formed near the distal tip will also be effective. The bulge is pushed sub-endocardially and during systole, the heart muscle 114 will "grab" onto the bulge and help to maintain position/placement of the sharp during substance delivery. A radiopaque marker 116 may also be 20 provided.

An alternative to the mechanical tissue engagement and dissection caused by the sharp in the above-described embodiments is to include a vacuum or suction device to adhere the distal end to the tissue. One of multiple lumens or the space between multiple catheters or probes will have a 5 vacuum applied and fix the device in place via suction. In other alternate embodiments one or more of the above-described features would be incorporated into a multi-component tip that has mechanically extendible/retractable elongated elements such as barbs, bristles, teeth or similar tissue engaging elongated elements. The multi-component tip can also 10 include irrigation, aspiration, vacuum, heat, coagulation or other functionalities.

Another aspect of preferred embodiments of the present invention is the control of the depth of penetration of the distal end structure. As discussed above, numerous constructions are available to penetrate tissue, 15 but in many instances, it will be desirable to know with a high degree of certainty that a maximum depth cannot be exceed. This factor is particularly important in percutaneous systems where it important that the myocardium remain unperforated, i.e., that the distal tip not penetrate the epicardium. One basic type of depth stop is illustrated in FIG. 12. In this embodiment the 20 distal end 120 may be of any construction, and a maximum depth of penetration d is defined from the distal tip back to a depth stop. The depth stop is a shoulder 122 formed by the juncture between the distal end 120 and a larger diameter section 124. In addition to serving a depth stop function,

the larger diameter section 124 will in some embodiments be an outgrowth of the desire to conduct a particular volume of fluid at a certain pressure and velocity, with the narrower section serving as a nozzle to change those characteristics just prior to delivery. In other embodiments, the larger 5 diameter will serve to permit a larger volume to be stored close to the distal end as well. The flat shoulder 122 connecting the two diameters serves to preclude the distal tip from exceeding the maximum penetration depth. Alternatively, other distal end configurations can include mechanical protuberances or other depth stop structures. As shown in FIG. 13, the distal 10 end 130 may be provided with wire loop "petals" 132 which provide a depth stop that is easily placed within a sleeve or outer catheter such as catheter 68 shown as in FIG. 7.

In addition to depth stops that mechanically define a distance between the distal tip and another portion of the distal structure, other techniques of 15 limiting the penetration depth are also contemplated in other embodiments. For example, radiopaque markers can be placed on a catheter or probe, and additional markers on the distal end of the structure. Such radiopaque markers are well known in the art. The relative position of the markers will provide an indication of the depth of penetration. Such an embodiment is 20 further useful in conjunction with mechanical depth stops. Also, as discussed above with reference to FIG. 3, if the distal end is advanced in an indexed fashion, manually or in an automated fashion, the depth of penetration will be determinable by the control of the distal end advancement precisely.

From the foregoing description of various distal end constructions, it can be seen that in certain embodiments of the present invention the fluid administered can provide a force useful in the administration procedure. In these embodiments, a fluid of appropriate viscosity is introduced either 5 through a single axial lumen or through one or more secondary lumens at a sufficient velocity and pressure. In some instances, it will be preferable to use a dissection fluid separate and apart from the angiogenic agent, which can be accomplished using a multiple lumen device. Multiple lumen delivery devices are well known in the art, and two typical cross-sections are 10 illustrated in FIGS. 14 and 15. In FIG. 14, the catheter 140 has a lumen which is bisected by a web 142 to create two lumens 144 and 146 of equal size. In FIG. 15, a catheter 150 has a single central lumen 152 and additional lumens 154 and 156 within the walls of the catheter defining the lumen 152. Variants of these two basic structures are known in the art. In addition to 15 fluids, certain of the multiple lumens can be selected to carry sensors or active components such as laser fibers, lead wires to ultrasonic transducers or RF conductors.

FIGS. 16A and 16B illustrate another embodiment of the present invention having a catheter or probe 160 in which high pressure fluid is emitted from the distal end 162 to dissect tissue. The catheter 160 may be a 20 single lumen or multi-lumen catheter are useful. In the embodiments shown in FIGS. 16A-B, the angiogenic substance or another of the fluids that comprise part of the administered dose is forced out at sufficient velocity and pressure

such that an area of disturbance or dissection is created in the myocardium that is larger than the channel formed by the dissection of a penetrating distal tip alone. In one embodiment, the substance may be a chemical that ablates tissue, a chemical denervation agent or a combination of the two with a fluid to aid delivery. Thus, as seen in FIG. 16A, catheter 160 emits a jet of fluid 162 from the distal end 164 which impinges on a tissue section 166 disrupting the tissue. As seen in FIG. 16B, a combination of this tissue disruption and mechanical dissection result in the penetration of the distal end 164 into the tissue. If a dual lumen delivery device such as that illustrated in FIG. 14 is employed, the fluid stream 162 that creates the dissection may be selectively stopped and an angiogenic agent can be emitted from orifices 168 which are in fluid communication with another lumen (not shown) within the catheter 160 as shown by the arrows. This embodiment will be particularly useful when it is determined that the sharp needs to be eliminated from the distal tip. The high velocity fluid stream 162 impinges on the tissue 166, creating a channel 168 formerly created solely by dissecting distal end 164. During the process fluid stream 162 alternately or optionally provides deposition of an angiogenic agent or dissection fluid alone that serves as a precursor to deposition. Additionally, in other embodiments similar to that shown in FIGS. 16A-B where radial orifices are provided in the distal end lateral fluid flow, e.g. liquids or gases like CO₂ can be forced through the orifices and multiple jets will create dissection planes and other collateral damage. Additionally, by selective administration of the appropriate fluid,

tissue can be either ablated or denerved. Such embodiments and administration methods will be employed to create sites more receptive to many of the angiogenic agents contemplated for use with the present invention. Preferably, several lateral orifices will permit the angiogenic agent 5 to be simultaneously delivered at several depths within the myocardium. Finally, as explained in detail above with reference to FIG. 10, if the lateral orifices are disposed at angles such that their discharge axes are inclined toward the tissue surface the backwards-firing "jets" will help to push the device into the tissue or at least assist to secure it within the surrounding 10 tissue when the device is inserted into the myocardium.

Another alternate technique to ensure stable placement of the distal end of the delivery device is to heat a portion of the distal end of the device. This heating may be to a temperature sufficient to ablate tissue, but may be much lower so long as the "hot tip" causes the distal end to "stick" to the 15 tissue in order to maintain placement during substance delivery. Any of a number of heat transfer techniques can be used, either by transmission of energy through the catheter or intraoperative probe or via absorption of energy emanating from an extracorporeal source.

Another aspect of the present innovation is the visualization of the 20 angiogenic agents both while in the reservoir, in situ during administration and in vivo after administration. In order effect visualization of the bolus of delivered substance, it is contemplated that, as explained above, in preferred embodiments, the angiogenic agent or a diagnostic material or other

substance be radiopaque. Referring to FIG. 17, a catheter 170 has a conduit 172 which is filled with one or more substances, preferably separated by marker substances. In the example illustrated, a carrier fluid 174 fills a section of the device. A radiopaque marker substance 176 precedes a dose 5 of the angiogenic agent 178, which in turn is followed by carrier fluid 174, thereby separating doses. The portion of the conduit 172 distal of the angiogenic agent 178 is preferably filled with the radiopaque marker substance 176 to provide imaging/navigation. However, alternatively the radiopaque marker substance 176 can be the angiogenic substance itself, in 10 which case the clear demarcation seen in FIG. 17 will not be present. Alternatively, as shown in FIG. 17, a length of a separate radiopaque or other marker substance 176 that can be expressed prior to delivery of the angiogenic agent to the tissue may be provided.

In any of the embodiments of FIG. 17, the radiopaque fluid or other 15 marker substance, allows the physician to visualize delivery of the appropriate volume of drug by visualizing the advance of the radiopaque separators. When the angiogenic agent is delivered, the radiopaque fluid will be flushed from tube, and thus it will be known that a full dose has reached tip of 20 delivery tube and there will be no waste or excess administration. In certain embodiments, where the angiogenic agent is a semi-solid "pellet" instead of a liquid, the pellet itself is preferably radiopaque. In any of these embodiments, another function served by the administration of a radiopaque marker with the angiogenic agent will be to mark the regions of deposition so that a

surrounding area of the tissue region may be properly treated with other doses.

Alternatively or in conjunction with an administered substance, the device itself can be made visible by the inclusion of radiopaque markers, 5 which is illustrated in FIGS. 4-5 and well known by those skilled in the art

As disclosed in U.S. patent application Serial No. 08/438,512, filed June 7, 1995, which is incorporated herein by reference, it is advantageous to place an angiogenic agent into the sites where energy has been introduced to cause revascularization in a TMR procedure. It is believed, based upon 10 preliminary data, that delivery of an angiogenic agent to a TMR site results in the most potent neovasculogenesis. TMR causes tissue damage in a region surrounding the site where energy has been introduced. Various energy sources have been used for TMR including laser energy, RF energy and ultrasonic energy. It is believed that the tissue damage provides benefits by 15 denervating tissue and that it also stimulates new blood vessel growth. The new blood vessel growth stimulated by TMR is apparently enhanced or supplemented by the introduction of an angiogenic agent to the TMR site.

Conversely, the administration of growth factors alone may not be optimal. Thus, in one preferred embodiment an optical fiber or RF electrode is 20 delivered down a central lumen of a first delivery catheter and then withdrawn and replaced by a delivery tube, which is then used to administer an angiogenic agent according to any of the techniques set forth above. Alternatively, the physician can leave the first delivery catheter in place and

deliver an angiogenic agent through the lumen of the first delivery catheter to the TMR site. Alternatively, multiple lumen embodiments such as those shown in FIGS. 14-15 permit energy and angiogenic agents to be delivered sequentially, along with marker substances and other fluids as previously described.

5

In terms of the adjunctive (with TMR) embodiments of the present invention, the introduction of energy to a tissue site includes all forms of TMR, whether the "channel" traditionally described is formed or not. Additionally, the adjunctive use described herein includes the application of 10 energy to merely disturb or disrupt the tissue. The enhancement of neovasculogenesis may occur due to subtle tissue effects. Such tissue effects may be stimulated by limited energy introduction, such that, in contrast to traditional TMR, no "channel" is formed. Such limited energy deposition may only serve to disturb or disrupt tissue locally while enhancing 15 the uptake of angiogenic agents. For example, a device with a heated distal tip would be used in place of either a sharp or a TMR channel forming device in certain embodiments, e.g., the distal construction shown in FIGS. 16A-B. This use may be preferable in cases where a simple injection or penetration does not create the disruption of the other techniques discussed above. In 20 other embodiments, the addition of non-thermal energy, particularly ultrasound or acousto-optic affects can be used to drive the angiogenic agent into the surrounding tissue or activate or alter the characteristics of the

20

substance, including in certain embodiments, using adjunctive energy to fracture microspheres containing angiogenic agent.

The present invention also encompasses methods of administering an angiogenic agent. In methods performed in accordance with the present invention, a delivery device is placed in contact with a heart wall and a dose of an angiogenic agent is introduced into the heart tissue. The administration may be timed to the heart cycle, and the step of placing the delivery device in contact with the heart wall can be preceded by piercing the wall. In certain adjunctive embodiments, the step of administering the angiogenic agent is performed after a the delivery of energy has disturbed the tissue, or in some cases the step of administering the angiogenic agent follows the step of performing TMR.

Although certain embodiments of the present invention have been set forth herein and described with particularity, these are provided for purposes of illustrating the present invention and are not limiting. Upon review of the foregoing description, those skilled in the art will realize that numerous adaptations, modifications and variations of the embodiments set forth herein are readily made without departing from the spirit of the inventions described. For these reasons, the scope of the present invention can be ascertained only by reference to the appended claims.

WHAT IS CLAIMED IS:

1. Apparatus for delivering a dose of an angiogenesis substance to a desired region of a patient's heart comprising an elongated shaft having a proximal end, a distal end configured to penetrate the desired region of the patient's heart, a handpiece proximal to the distal end, a reservoir containing an angiogenesis substance, an inner lumen extending within the elongated shaft to the distal end which is in fluid communication with the reservoir of angiogenic substance, and at least one discharge port in the distal end for delivering angiogenesis substance into the region of the patient's heart.
- 10 2. The apparatus of claim 1 wherein the elongated shaft is a catheter.
3. The apparatus of claim 1 wherein the elongated shaft is an intraoperative probe.
- 15 4. The apparatus of claim 1, further comprising a metered dispensing system.
5. The apparatus of claim 4, wherein the metered dispensing system further includes dispensing control.
6. The apparatus of claim 5, wherein the dispensing control is disposed on the handpiece.
- 20 7. The apparatus of claim 5, wherein the dispensing control is automated.
8. The apparatus of claim 7 wherein the dispensing system includes a signal receiver to detect signals generated by the heart and a circuit

which synchronizes the activation of the automated dispensing apparatus in response to heart signals received by the signal receiver.

9. The apparatus of claim 8 wherein the synchronizing circuit inhibits activating the dispensing apparatus during a pre-determined portion of the heart cycle.

10. The apparatus of claim 1 wherein the distal end of the shaft further comprises at least one sharp.

11. The apparatus of claim 1 wherein the distal end comprises one or more radially oriented orifices.

10 12. The apparatus of claim 11 wherein the distal end further comprises one or more elongated elements that deploy from a first position that inhibits tissue engagement by the distal end to a second position that permits tissue engagement by the distal end.

13. The apparatus of claim 11 wherein the distal end comprises at 15 least one barb aligned with a longitudinal axis of the elongated shaft and disposed along an outside surface of the elongated shaft.

14. The apparatus of claim 13 wherein the barb deploys from a first portion that inhibits tissue engagement to a second position that permits tissue engagement.

20 15. The apparatus of claim 1 wherein the distal end has a bulbous section.

16. The apparatus of claim 15 wherein the bulbous section is inflatable.

17. The apparatus of claim 1 wherein the distal end has a radiopaque marker.

18. The apparatus of claim 1 wherein the elongated shaft has a depth stop to control the depth of penetration of the distal end into the heart tissue.

5 19. The apparatus of claim 18 wherein the distal end comprises a first distal section, a second proximal section having larger transverse dimensions than the first distal section and a shoulder connecting the distal and proximal sections which comprises the depth stop.

10 20. The apparatus of claim 18, wherein the depth stop comprises one or more mechanical elements that extend radially outward from the distal end.

21. The apparatus of claim 1 wherein the elongated shaft has at least one additional lumen.

15 22. The apparatus of claim 21 wherein at least one of the plurality of lumens is in fluid communication with a source of a fluid other than an angiogenic agent.

23. The apparatus of claim 1 including a distal tissue contact device for tissue injury.

20 24. The apparatus of claim 23 wherein the distal tissue contact device for tissue injury is a mechanical device affixed to the distal end.

25. The apparatus of claim 23 wherein the distal tissue contact device for tissue injury is a laser energy conductor.

26. The apparatus of claim 23 wherein the distal tissue contact device for tissue injury is an RF energy conductor.

27. The apparatus of claim 23 wherein the distal tissue contact device for tissue injury is an ultrasound transducer.

5 28. The apparatus of claim 23 wherein the distal tissue contact device for tissue injury includes a conduit connected to a source of fluid which can be delivered at a pressure and velocity sufficient to disrupt tissue.

29. The apparatus of claim 23 wherein the distal tissue contact device is an electrical current conductor.

10 30. The apparatus of claim 21 including a distal tissue contact device for tissue injury slidably disposed within one of said additional lumens.

31. An apparatus for injection of at least one dose of an angiogenic agent to a patient's heart which is synchronized to a cardiac cycle of the patient's heart, comprising:

15 an injection device;

an elongated shaft having a proximal end connected to the injection device and at least one lumen extending within the elongated shaft in fluid communication with the injection device; and

20 a solenoid connected to the injection device to control the dosage amount of angiogenic agent dispensed by the injection device when the solenoid is pulsed by a signal related to the cardiac cycle of the patient's heart.

32. The apparatus of claim 31 wherein the solenoid controls the same amount of angiogenic agent dispensed after each of one or more pulses.

33. The apparatus of claim 31 further comprising an energy probe in contact with heart tissue and a switch for activating the energy probe, whereby energy is introduced into the heart tissue by operation of the activation switch.

34. The apparatus of claim 33 wherein the energy probe is a laser fiber.

35. An apparatus for delivering a substance comprising a delivery lumen extending from a distal end to a proximal point, and wherein at least a first section of the delivery lumen is filled with the angiogenic substance.

36. The apparatus of claim 35 further comprising a second section of the delivery lumen in fluid communication with the first section and containing a substance other than an angiogenic agent.

37. The apparatus of claim 35 wherein the angiogenic agent is a fluid.

38. The apparatus of claim 35 wherein the delivery lumen contains at least an angiogenic agent, a fluid and a marker substance.

39. The apparatus of claim 35 further comprising at least a second lumen.

40. A method of administering an angiogenic agent to a wall of a patient's heart, comprising the steps of:

penetrating the patient's heart wall with a distal end of an administration device which has at least a pre-determined amount of angiogenic agent;

5 activating the administration device so as to deliver a pre-determined amount of an angiogenic agent into the patient's heart wall.

41. The method of claim 40 further comprising the steps of:

monitoring a cardiac cycle and creating a signal representative of the cardiac cycle; and

10 synchronizing the activation of the administration device in response to the signal.

42. The method of claim 40 including the step of contacting the heart wall with an energy delivery device prior to the step of activating the administration device.

15 43. The method of claim 42 wherein the step of contacting the heart wall further comprises the step of delivering energy to the heart wall to disturb tissue in the heart wall.

44. The method of claim 43 wherein the step of delivering energy performs a transmyocardial revascularization procedure.

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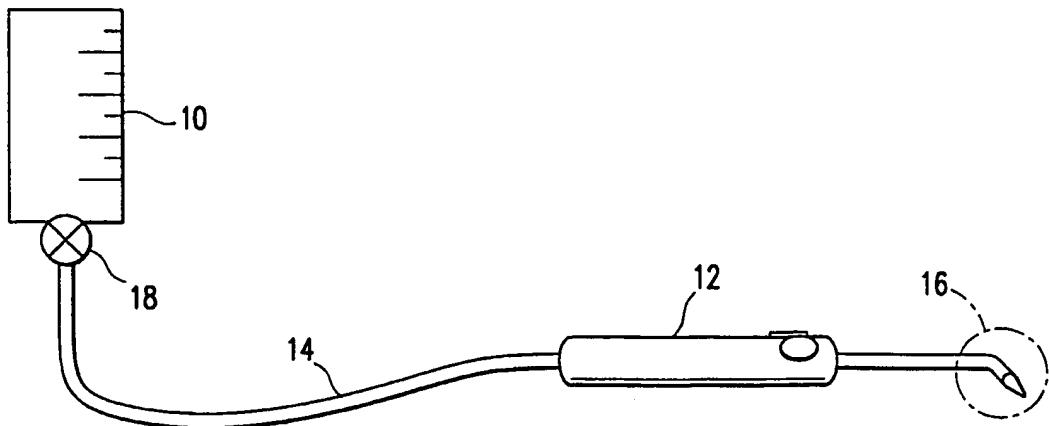


FIG. 1

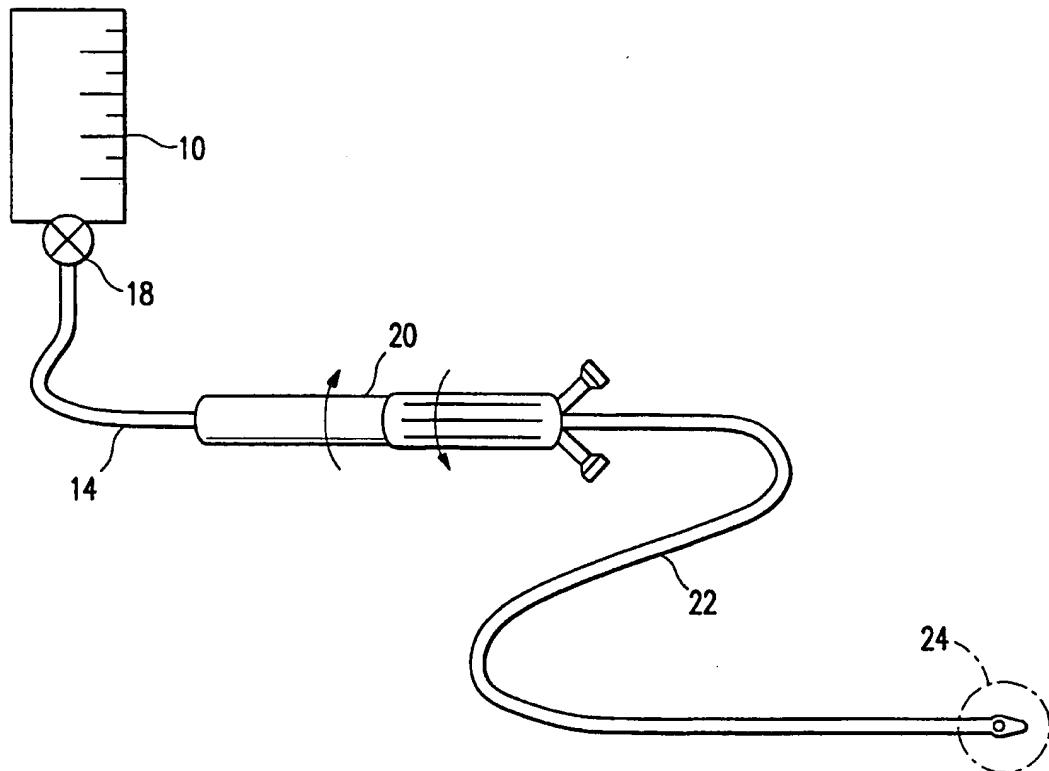


FIG. 2

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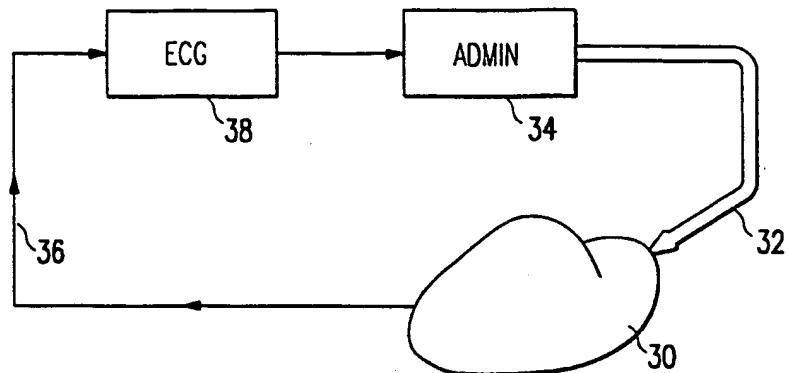


FIG. 3

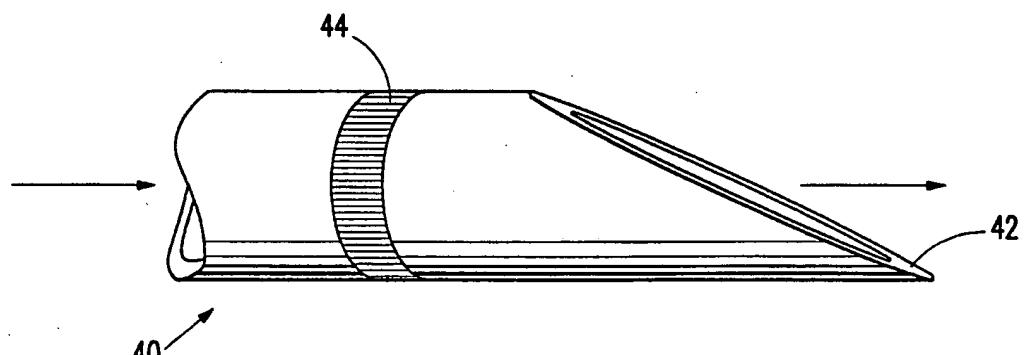


FIG. 4

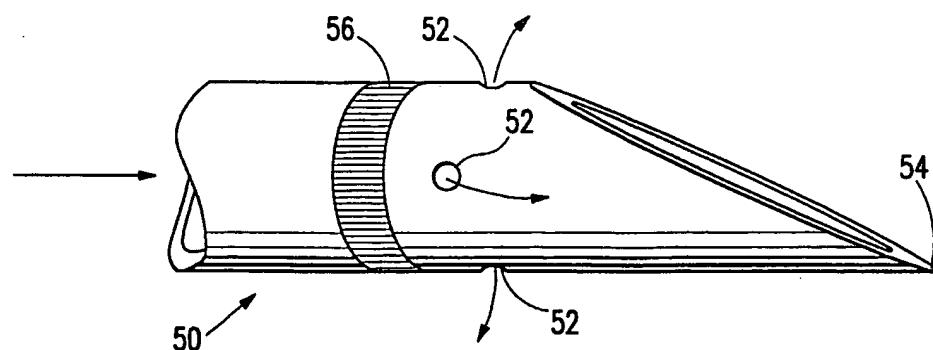


FIG. 5

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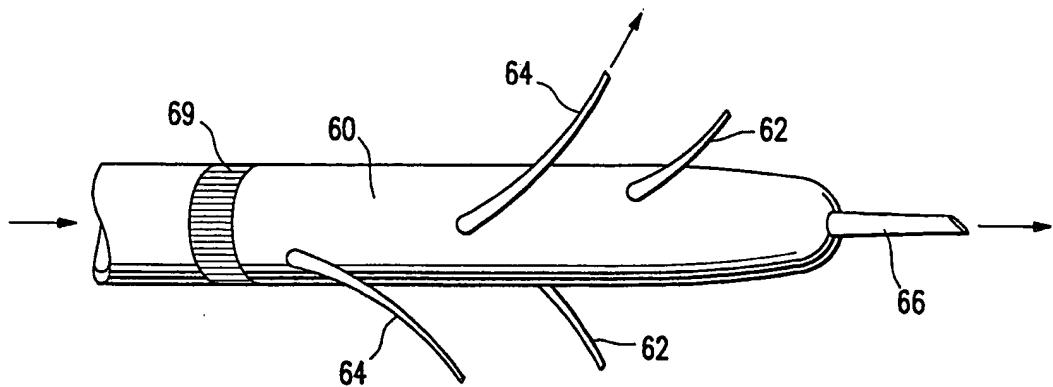


FIG. 6

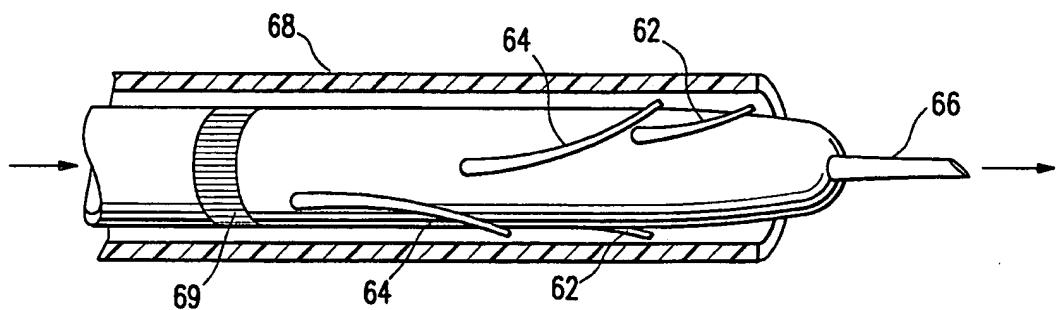


FIG. 7

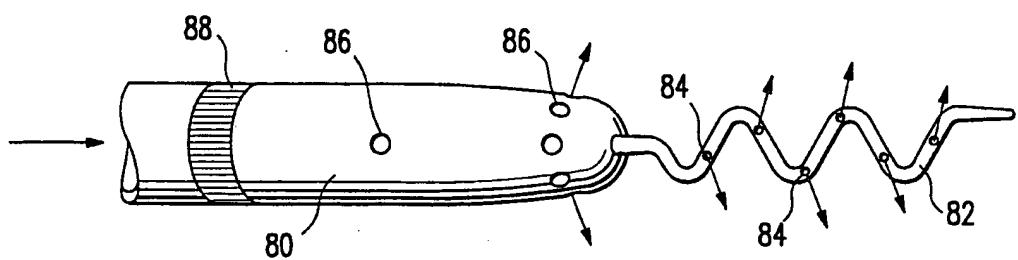


FIG. 8

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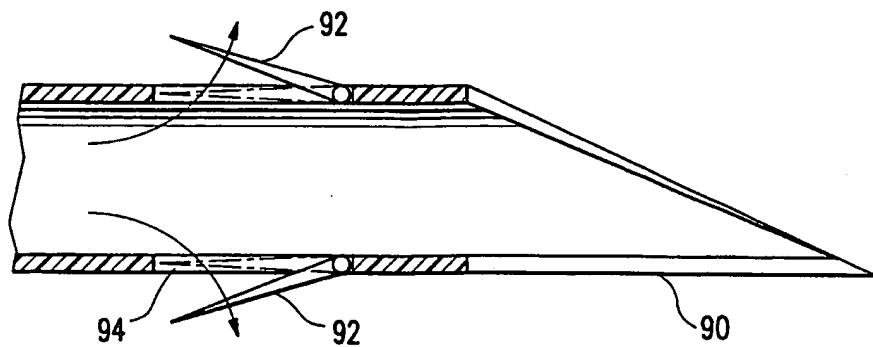


FIG. 9

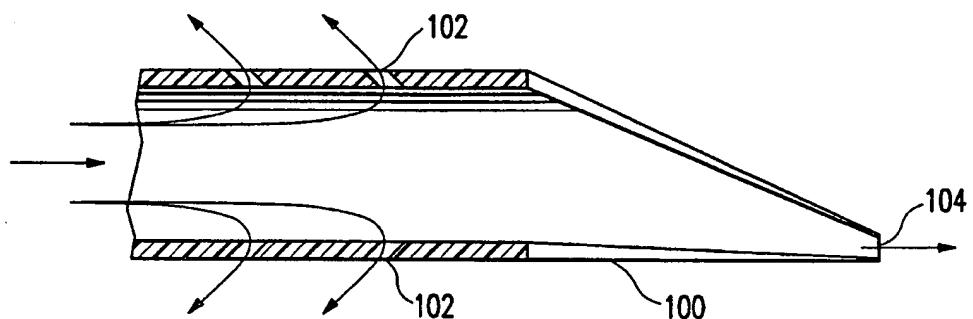


FIG. 10

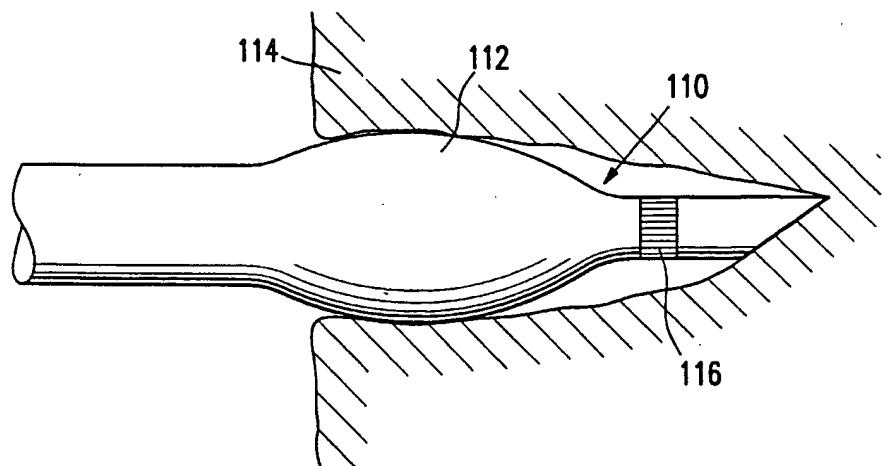


FIG. 11

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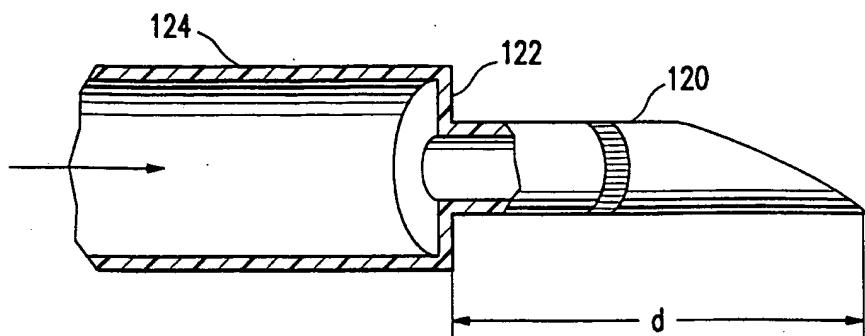


FIG. 12

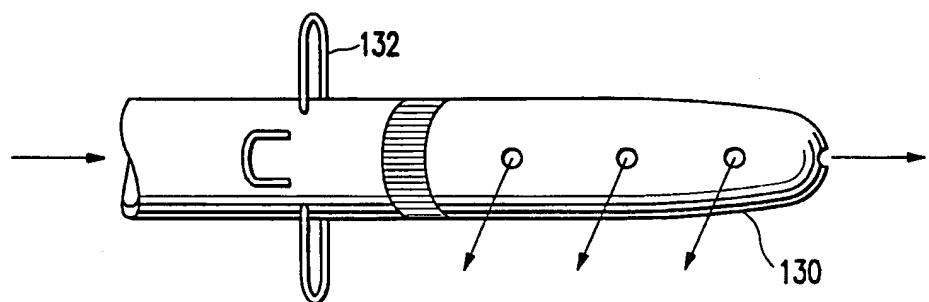


FIG. 13

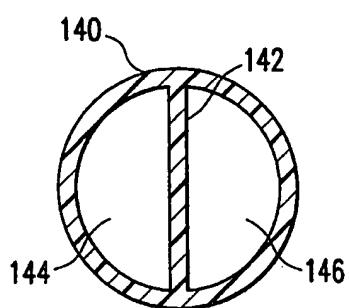


FIG. 14

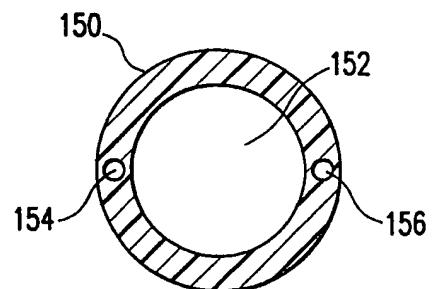
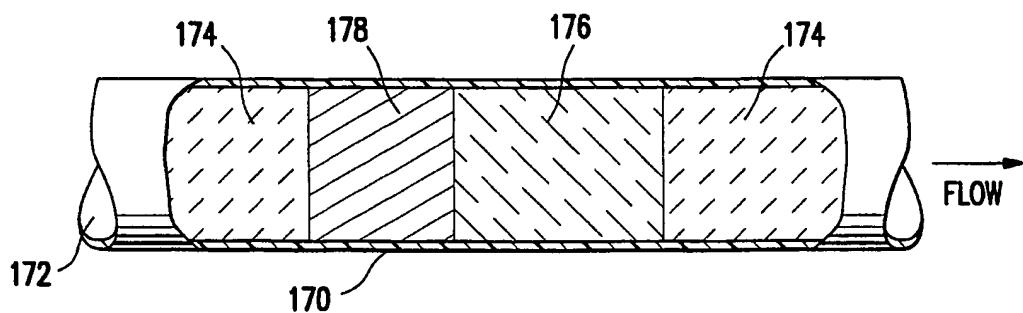
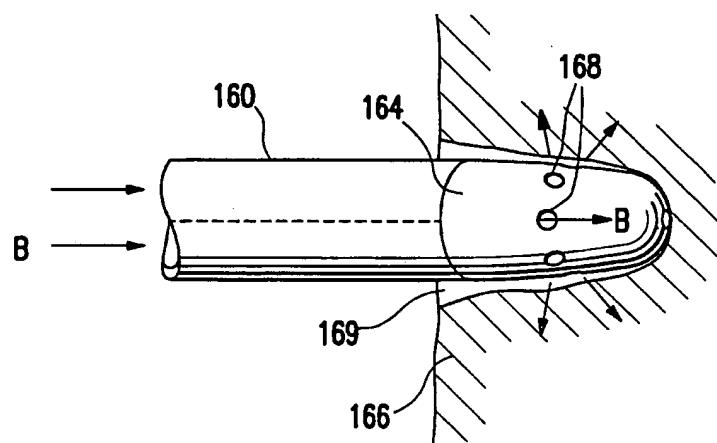
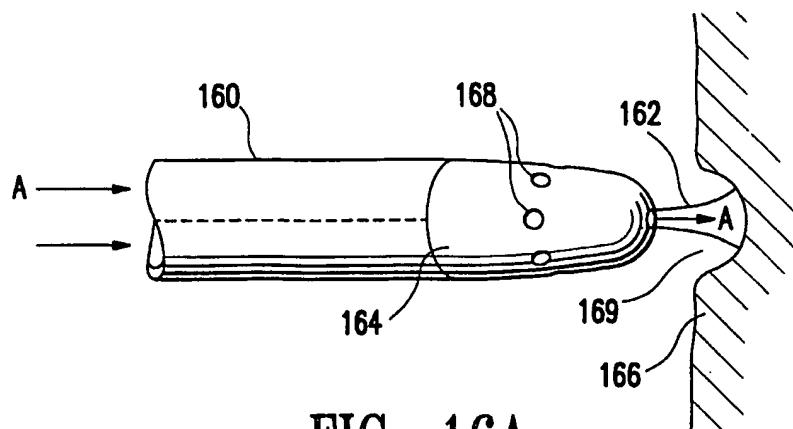


FIG. 15

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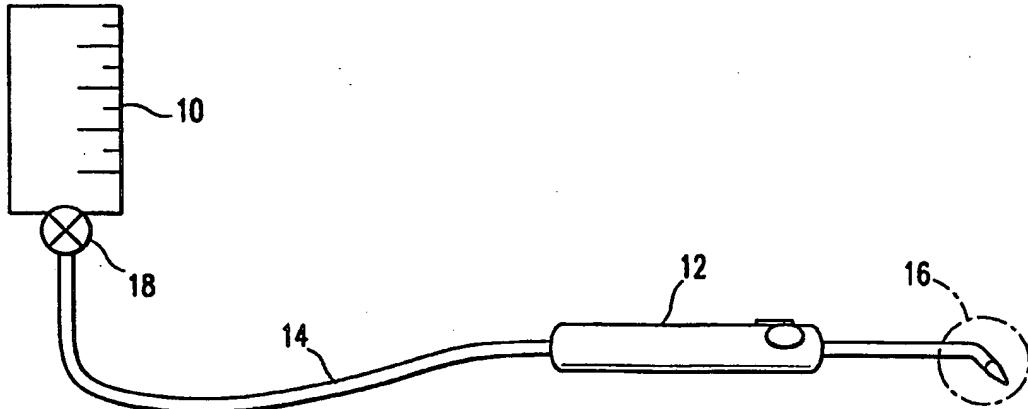




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(54) Title: DELIVERY OF AN ANGIOGENIC SUBSTANCE



(57) Abstract

Using either a percutaneous, intraoperative or minimally invasive approach, an elongated member containing an angiogenic agent is guided to a heart wall and the agent is dispensed into heart tissue. The administration of the angiogenic agent can be automated and controlled so as to be synchronized with respect the cardiac cycle. The device has a distal end configured to dissect heart tissue and penetrate into the myocardium. Additional fluids or substances can be dispensed in combination with the angiogenic agent to provide visualization and site mapping. In certain embodiments, the angiogenic agent is delivered adjunctively with the administration of energy, such as laser energy or RF energy which disturbs the heart tissue sufficiently to enhance the effects of the agent. There is also disclosed a device for administering an angiogenic agent that contains the angiogenic agent and additional fluids such as a marker within a single conduit.

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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 99/07081A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M25/00 A61B17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61M A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0 853 921 A (ECLIPSE SURGICAL TECH) 22 July 1998 (1998-07-22) page 18, line 26 -page 24, line 45; figures 1-18 ---	1-7,10, 11, 17-19, 21-25,30
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X	WO 98 05307 A (LOCALMED INC) 12 February 1998 (1998-02-12) the whole document ---	1-3, 21-27,30
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 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

6 August 1999

29. NOV. 1999

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07081

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US 5 431 649 A (HOEY MICHAEL F ET AL) 11 July 1995 (1995-07-11) the whole document ---	1,2,10, 11,23, 24,26,28
X	US 5 713 853 A (CLARK DAVID W ET AL) 3 February 1998 (1998-02-03) column 5, line 1 -column 7, line 12; figures 1-4 column 12, line 6 - line 25; figures 16-19 ---	1,11,12, 17,21,22
A	EP 0 150 960 A (CEDARS SINAI MEDICAL CENTER) 7 August 1985 (1985-08-07) page 7, line 25 -page 12, line 5; figures 1-7 -----	1,4,5, 7-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/07081

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 40-44 because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
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Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
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1-30

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-30

Apparatus to deliver dose of angiogenesis substance to region of heart comprising elongated shaft with inner lumen and a distal end to penetrate heart with discharge port, handpiece and reservoir.

2. Claims: 31-34

Apparatus to inject angiogenic substance into heart synchronized with the heart cycle comprising injection device, elongated shaft with inner lumen and solenoid.

3. Claims: 35-39

Apparatus to deliver a substance comprising delivery lumen with a first section filled with angiogenic substance.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat''l Application No

PCT/US 99/07081

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